bin agents, such as hirudin and argatroban can be used for the management of this syndrome, because of lack of pharmacologic antagonists, bleeding is still a problematic issue. Previously, ReoPro (Centocor, Malvern, PA), a glycoprotein IIb/IIIa antibody, has been shown to blunt the HIT response. However, this drug cannot be administered for an extended period of time. Ticlopidine (Ticlid, Sanofi Winthrop, Malvern, PA) represents an antiplatelet drug targeting ADP receptors on platelets. To determine the effect of this drug on platelet activation, sera collected from HIT confirmed patients (n = 62) were screened in the platelet aggregation assay. Ticlid produced a concentration dependent inhibition of platelet activation producing a marked inhibition of HIT induced platelet activation at 25–50 μg/ml. Similarly in the ^{14}C serotonin release assay Ticlid produced a complete inhibition at equivalent concentrations. Blood obtained from patients receiving Ticlid (n = 6) did not result in platelet activation with HIT positive sera. Similarly, the platelets from these patients failed to release ^{14}C serotonin. At a comparable level a soluble form of aspirin (Aspisol, Bayer, Germany) failed to produce similar effects in the HIT screening assays. These studies suggest that Ticlid can be considered in the management of patients with HIT or for prophylactic use in patients at high risk for HIT.

2:15

712-2 Antiplatelet Efficacy of Orally Administered DMP802, a GPIIb/IIIa Receptor Antagonist, in the Conscious Dog

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DMP802 is a novel antiplatelet agent with high affinity and specificity for the platelet glycoprotein IIb/IIIa receptor. DMP802 inhibits ADP-induced aggregation of human and canine platelets *in vitro* with an IC_{50} of 29 and 44 nmol/L, respectively. DMP802 shows affinity for activated as well as resting platelets. In activated human or canine gel-purifed platelets, DMP802 inhibited 125I-fibrinogen binding with an IC_{50} of 0.0089 and 0.01 μmol/L, respectively. DMP802 is selective for the GP IIb/IIIa receptor over the $\alpha v\beta 3$, the $\alpha 4\beta 1$, and the $\alpha 5\beta 1$ receptors. After intravenous administration to conscious dogs, DMP802 (0.025 mg/kg) inhibited platelet aggregation induced by 100 μmol/L ADP by approximately 90%. DMP802 (0.05–0.2 mg/kg PO) dose-dependently inhibited *ex vivo* platelet aggregation induced by ADP without affecting platelet number. After a 0.1 mg/kg oral loading dose, followed by four consecutive once daily doses of 0.025 mg/kg, antiplatelet activity was observed in the range of 50–95% inhibition of platelet aggregation (with the exception of the 96-hour timepoint). After five consecutive daily doses of DMP802 at 0.05 mg/kg PO, greater peaks and troughs were noted in the aggregation curves than when the loading and maintenance doses (0.1 and 0.025 mg/kg PO) were given. Inhibition of platelet aggregation ranged between 20 and 80%. In summary, DMP802 is an orally active antiplatelet agent which is effective following either a single or repeated daily oral administration to conscious dogs.

2:30

712-3 Low-Shear Platelet Adhesion is Inhibited by GP IIb/IIIa Antagonist DMP-728

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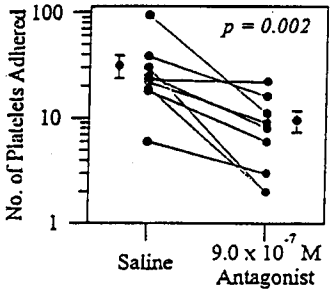
Although glycoprotein (GP) IIb/IIIa receptors do not play a significant role in high-shear platelet adhesion, they may contribute to adhesion in low-shear areas that occur distal to coronary artery stenoses.

We studied low-shear platelet adhesion and aggregation in 10 healthy subjects following the addition of GP IIb/IIIa antagonist DMP-728 (Merck) or saline to platelet-rich plasma (PRP) in random order. Platelet adhesion was measured using Born aggregometry. The chamber, which utilizes a fibronectin-coated slide, was perfused with PRP at a shear rate of 25 s^{-1}. The number of adherent platelets was determined after 7 minutes of perfusion. As shown, low-shear platelet adhesion was significant reduced (70%) by DMP-728 compared to saline. Platelet aggregation was also significantly reduced (65%) by DMP-728.



Conclusion: These data suggest that GP IIB/IIIa antagonists may achieve their anti-thrombotic effect not only through inhibition of aggregation, but also through inhibition of low-shear platelet adhesion.

2:45

712-4 Captopril Reduces Thrombus Formation in Early Postmyocardial Infarction Stage

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Long-term administration of the angiotensin-converting enzyme inhibitor captopril (C) in survivors of myocardial infarction (MI) reduces the risk of death, recurrence of MI and unstable angina, suggesting that C may have some antithrombotic properties. We assessed the effects of short-term C administration on platelet (P) interaction with denuded subendothellium by means of an "ex vivo" perfusion system (Baumgartner chamber) in 25 patients (Pts) (22 men, mean age 62 ± 5 years). P aggregation was tested by conventional turbidometric procedures in response to several inductors (Arachidonic acid, ADP, Collagen, ristocetin, epinephrine, synthetic thromboxane-endoperoxide analogue -V46619). Blood samples were withdrawn after 5 days of MI (as baseline determination) and after a mean of 12 ± 3 days of treatment with C (n = 13) or placebo (n = 12). Results were expressed as a percentage of damaged vessel surface covered by platelets (%SCP) and by thrombi (%SCT). Thrombus: P aggregates of >5 μ.

	% SCT		% SCP	
	Baseline	Post	Baseline	Post
C	64 ± 24	36 ± 25[a)]	24 ± 10	17 ± 4
Placebo	56 ± 21	67 ± 15[b)]	18 ± 8	21 ± 6

[a)] $p < 0.05$ (baseline vs post); [b)] $p < 0.008$ (C vs placebo)

Aggregometric response to inductors showed no significant variation between the two groups and there were no changes in % SCP between C and placebo, however, C markedly reduces thrombus formation in an "ex vivo" perfusion model, suggesting an effect on P performance that may contribute to its beneficial effects after MI.

3:00

712-5 Phosphatidylinositol 3-Kinase Inhibition: A most Potent Approach to Inhibit Human Smooth Muscle Cell Growth

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Smooth muscle cell (SMC) growth plays an important role in vascular diseases such as restenosis and coronary venous bypass graft disease. Important factors include platelet-derived growth factor-BB (PDGF-BB). Activation of phosphatidylinositol 3-Kinase (PI-3K) by PDGF receptor is implicated in cell growth. The effects of a specific inhibitor of PI-3K, wortmannin, on growth of human SMC was studied and compared with other growth inhibitors.

SMC were cultured from SV obtained during surgery. Cell proliferation was assayed by ^{3}H-thymidine incorporation. PDGF-BB (5 ng/ml) stimulated ^{3}H-thymidine incorporation (6-fold) in SMC from both men and women (n = 10). The proposed growth inhibitors dexamethasone, somatostatin, forskoline, nitric oxide donors (SNAP, nitroglycerin) and C-typ natriuretic peptide (10^{-9} to 10^{-6}M) had no inhibitory effects on ^{3}H-thymidine incorporation. The L-type (verapamil; 10^{-6}M) and T-type (mibefradil; 10^{-9}M) calciun channel blockers inhibited ^{3}H-thymidine incorporation (42% and 48% inhibition, respectively) only in SMC from women (n = 6), while wortmannin, the PI-3K inhibitor, markedly inhibited ^{3}H-thymidine incorporation in SMC from both men and women (60% inhibition; n = 14). Simvastatin and fluvastatin also had some inhibitory effect, but with less potency (30% inhibition; n = 18).

Thus, inhibition of PI-3K is most efficient to inhibit SMC growth. Development of specific inhibitors of PI-3K would have great clinical impact in therapy of restenosis and bypass graft disease.